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| EXAMINER |
|---|
| WANG, SHENGJUN |

| ART UNIT | PAPER NUMBER |
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| 1617 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/788,413 | ANDERSON ET AL. | |
| | Examiner | Art Unit | |
| | Shengjun Wang | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-29,75-78,81,83-91 and 93-111* is/are pending in the application.

4a) Of the above claim(s) *2,4,15-17,27-29,75-78 and 81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-14,18-26,83-91,93-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Receipt of applicants' amendemnts, remarks and the 1.132 declaration submitted March 20, 2008 is acknowledged.

### *Claim Rejections 35 U.S.C. 102*

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1, 3, 5-8, 10-12, 22, 95, 106, 107 and 110 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 5320413 (IDS).

3. JP 5320413 discloses an dantrolene sodium suspension comprising about 1-50 mg/ml of dantrolene sodium, particular examples disclosed are with a concentration of 1 mg/ml and 5 mg/ml. The composition further comprising carboxylic salt, such as sodium citrate, sodium tartrate, etc. see the entire document, particularly, columns 5-6. As to the limitation of "safe for injection," note since '413 disclosed a pharmaceutical composition, it would have been reasonably expected it is be safe for injection, absent evidence to the contrary. Note, when the reference discloses all the limitations of a claim except a property or function, and the examiner cannot determine whether or not the reference inherently possesses properties which anticipate or render obvious the claimed invention but has basis for shifting the burden of proof to applicant as in In re Fitzgerald, 619 F.2d 67, 205 USPQ 594 (CCPA 1980). See MPEP § § 2112- 2112.02. The carboxylic acid salts would meet the limitation of water soluble surfactant. Note, the composition does not have mannitol.

***Claim Rejections 35 U.S.C. 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 3, 5-14, 18-26, 83-91, 93-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. (IDS), in view of Patel et al. (6,294,192), Ramstack et al. (US 6,495,164), Bosch et al. (US 5,510,118), and JP 5320413( IDS).

6. Ellis teaches dantrolene sodium is an old and well known therapeutical agent, and is known to be administered by any conventional method. The dosage amount is known to be in the range of up to 139 mg/kg of body weight per day. See, particularly, col. 1, lines 10-66, col. 4, lines 1-5.

7. Ellis et al. do not teach expressly the particular composition in high concentration, or be capable of being formulated to a composition in high concentration, or the particular pharmaceutical acceptable carrier and excipients.

8. However, Patel et al. teaches a pharmaceutical composition and method for delivery of hydrophobic therapeutical agents, such as dantrolene sodium, the composition comprise the therapeutical agent, solubilizer, and surfactants, wherein the solubilizer may be alcohols, such as ethylene glycol, propylene glycol, glycerol, polyethylene glycol (PEG 200-600); amide, such as dimethylacetamide, or mixture thereof. The amount of solubilizer is not particularly limited. The composition may be in the form of solution (diluted preconcentrate), semi-solid dispersion, or multiphase dispersion. The composition may be formulated into various forms suitable for

conventional delivery, including oral, topical, transdermal, ocular, parenteral, etc. See, particularly, the abstract, column 24, line 31, col. 25 line 15 to col. 28, line 24, and the claims. For multi-phase dispersion, the solid phase may be in milled, micronized forms. See, particularly, col. 27, lines 11-42. Patel further disclosed that, for dispersion, the particle size is typically less than 20 nm. See, col. 28, line 44 to col. 29, line 4. Ramstack et al. teaches an improved injectable suspension with a concentration of more than 30 mg/ml, wherein the composition is characterized by containing surfactants. See, particularly, the abstract and the claims. Bosch et al. teaches a suspension composition suitable for parenteral administration, comprising water-insoluble nanoparticle therapeutical agent, wherein the average particle sized is about 400 nm and a surface modifier. Suitable surface modifiers include benzalkonium chloride. See, particularly, the abstract, and the claims. JP 5320413 teaches a dantrolene sodium suspension comprising about 1-50 mg/ml of dantrolene sodium, see the entire document, particularly, columns 5-6.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to make a concentrated dantrolene sodium composition herein by method known in the art, such as incorporate the known pharmaceutical carrier, and/or excipients polyethylene glycol, dimethylacetamide, and/or benzalkonium chloride, either in solution, or in suspension.

A person of ordinary skill in the art would have been motivated to make a concentrated dantrolene sodium composition herein by method known in the art, such as incorporate the known pharmaceutical carrier, and/or excipients polyethylene glycol, dimethylacetamide, and/or benzalkonium chloride, either in solution, or in suspension because dantrolene sodium is known

to be administered up to about 1000 mg per day (for patient with body weight of 75 kg) and make a high concentration composition is apparent for its convenience for administration. Further, concentration up to 50 mg/ml is known in the art. Further, method of making such concentrated composition is known in the art, as evidenced by the cited prior art, one of ordinary skill in the art would have been motivated to make such composition and enjoy a reasonable expectation of success. The employment of the particular combination herein is seen to be a selection from amongst equally suitable material and as such obvious, absent evidence to the contrary. Ex parte Winters 11 USPQ 2nd 1387 (at 1388). Further, The optimization of a result effective parameter, e.g., particle size for an injectable composition, is considered within the skill of the artisan. See, In re Boesch and Slaney (CCPA) 204 USPQ 215. As to the dry powder, one of ordinary skill in the art would have been motivated to make a dry powder, which upon reconstitution would yield the solution or suspensions, because of the obvious convenience for storage. As to claims 103-105 which recite steps of simply combining the ingredients and mixing the combination, note such mixing step would have been within the purview of ordinary skilled artisan.

***Response to the Arguments***

Applicants' amendments and remarks, and the 1.132 declaration submitted March 20, 2008 have been fully considered, but are not persuasive.

9. The declaration under 37 CFR 1.132 filed March 20, 2008 is insufficient to overcome the rejection of claims 1, 3, 5-14, 18-26, 83-91, 93-111 based upon Ellis et al. (IDS), in view of Patel et al. (6,294,192), Ramstack et al. (US 6,495,164), Bosch et al. (US 5,510,118), and JP 5320413( IDS) as set forth in the last Office action because: It states that the claimed subject

matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP § 716.04. Particularly, the declaration cite Karan reference as an unsafe example of previous attempt. Karan reference disclosed coated particles for injection. The coated particles are structurally different from what would have been suggested by the prior art on the record.

10. Applicants' amendments and remarks submitted March 20, 2008 have been fully considered, but are not persuasive.

11. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Particularly, The cited references teaches how to make a concentrated composition for injection of a water insoluble pharmaceutical agent. Further, it is known in the art that high concentrated dantrolene composition for injection is desirable. Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made, to make a high concentrated dantrolene composition for injection as suggested by the cited prior art. Note Patel et al. discloses that for suspension the particle size of 20 nm or less for effective transportation. Although the preferred embodiments in Patel et al is oral composition, the composition may also be formulated into compositions suitable for parenteral administration. (col. 26, lines 46-55).

Ramstack et al. was cited in the rejections to show that an improved injectable suspension with a concentration of more than 30 mg/ml, wherein the composition is characterized by containing surfactants. It is well settled that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

12. As to the establish of long felt need, note establishing long-felt need requires objective evidence that an art recognized problem existed in the art for a long period of time without solution. The relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors.

13. First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. In re Gershon, 372 F.2d 535, 539, 152 USPQ 602, 605 (CCPA 1967) ("Since the alleged problem in this case was first recognized by appellants, and others apparently have not yet become aware of its existence, it goes without saying that there could not possibly be any evidence of either a long felt need in the . . . art for a solution to a problem of dubious existence or failure of others skilled in the art who unsuccessfully attempted to solve a problem of which they were not aware."); Orthopedic Equipment Co., Inc. v. All Orthopedic Appliances, Inc., 707 F.2d 1376, 217 USPQ 1281 (Fed. Cir. 1983) (Although the claimed invention achieved the desirable result of reducing inventories, there was no evidence of any prior unsuccessful attempts to do so.).

14. Second, the long-felt need must not have been satisfied by another before the invention by applicant. Newell Companies v. Kenney Mfg. Co., 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988) (Although at one time there was a long-felt need for a "do-it-yourself" window

shade material which was adjustable without the use of tools, a prior art product fulfilled the need by using a scored plastic material which could be torn. "[O]nce another supplied the key element, there was no long-felt need or, indeed, a problem to be solved".)

15. Third, the invention must in fact satisfy the long-felt need. In re Cavanagh, 436 F.2d 491, 168 USPQ 466 (CCPA 1971.)

16. It is noted that Karan reference cited in the 132 declaration actually shows that MC-D high concentrated composition is safe for injection. See, the abstract, and the discussion at pages 801-802. Therefore, it appears that the problem has been solved. Further, as to the third aspect, it is noted that the evidence on the record has not shown that the claimed invention is better than the previous attempt and actually satisfy the long-felt need.

17. As to the rejections over JP 5320413, applicants' attention is directed to the claims and the embodiments 1-4. Note the claims do not require any of the injection unacceptable excipients. Further, embodiments 1-4 disclosed liquid examples comprising dantrolene suspension. There is no reasons why these composition are not suitable for injection.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang whose telephone number is (571) 272-0632. The examiner can normally be reached on Monday to Friday from 7:00 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shengjun Wang/
Primary Examiner, Art Unit 1617